Randomized Trial of Vaginal Prostaglandin E_2 Versus Oxytocin for Labor Induction in Term Premature Rupture of Membranes

Cigdem Kunt, Mine Kanat-Pektas*, Ayse Nur Cakir Gungor, Raziye Keskin Kurt, Mustafa Ozat, Cavidan Gulerman, Tayfun Gungor, Leyla Mollamahmutoglu

Department of Perinatology, Dr Zekai Tahir Burak Women Health Research and Education Hospital, Ankara, Turkey.

SUMMARY

Objective: The aim of this study was to compare the efficacy and safety of a prostaglandin E_2 (PGE_2) vaginal insert with those of oxytocin for labor induction. The present study also examined whether its use reduces the rate of cesarean delivery in term pregnancies with premature rupture of membranes (PROM) and low Bishop scores.

Materials and Methods: A total of 240 women with singleton pregnancies at ≥ 37 weeks, no prior uterine scar, vertex presentations, reactive nonstress tests, PROM for ≥ 12 hours and Bishop scores of ≤ 6 were randomly assigned to receive either oxytocin or vaginal PGE_2. The primary outcomes were time from induction to delivery and mode of delivery.

Results: The time from labor induction to active labor onset was significantly shorter in the oxytocin group than in the PGE_2 group (4.9 ± 4.1 *vs*. 8.5 ± 3.6 hours; $p = 0.02$). The time from induction to delivery was also significantly shorter in the oxytocin group (3.4 ± 1.5 *vs*. 9.6 ± 4.7 hours; $p = 0.02$). Cesarean delivery rates were statistically similar in the oxytocin and PGE_2 groups (18.3 *vs*. 20.0%; $p = 0.81$). Neonatal outcomes were comparable in both groups. Comparable results were observed for nulliparous women included in the study population.

Conclusion: Oxytocin treatment seems to be superior to vaginal administration of PGE_2 to induce labor in term pregnancies complicated with PROM and unfavorable services. [*Taiwan J Obstet Gynecol* 2010;49(1):57–61]

Key Words: Bishop score, labor induction, oxytocin, premature rupture of membranes, prostaglandin E_2

Introduction

Premature rupture of membranes (PROM) at term is described as the rupture of membranes prior to the onset of labor at or beyond 37 weeks of gestation. Approximately 10% of term pregnancies are complicated with PROM. Patients with PROM complain of fluid leakage, vaginal discharge, vaginal bleeding and pelvic pressure without any contractions [1,2].

Nearly 90% of women enter spontaneous labor within 24 hours when they experience PROM at term. The major question regarding the management of patients with PROM is whether to allow them to enter labor spontaneously or to induce labor. Although the management of patients with PROM usually depends on their personal wish, the major maternal risk at this gestational age is intrauterine infection [3,4].

The neonatal risks associated with expectant management of PROM include infection, placental abruption, fetal restriction deformities, pulmonary hypoplasia, distress, and related fetal/neonatal death. Fetal death occurs in about 1 in 1,000 women with term PROM who have been expectantly managed. Because the risk of intrauterine infection increases with the duration of PROM, the induction of labor decreases the risk of chorioamnionitis, without changing the rate of cesarean delivery, as opposed to expectant management [1–4].

The sustained-release prostaglandin E_2 (PGE_2) vaginal insert has been shown to be safe and efficacious in

*Correspondence to: Dr Mine Kanat-Pektas, Department of Perinatology, Dr Zekai Tahir Burak Women Health Research and Education Hospital, Ertugrul Gazi Mahalle, Kutlugun Sokak, No. 37/14, 06590 Iccebeci, Ankara, Turkey.
E-mail: minekanat@hotmail.com
Accepted: April 2, 2009

promoting cervical ripening in women with term pregnancies and low Bishop scores [5]. However, there are insufficient data related to the efficacy and safety of PGE_2 in term pregnancies complicated with PROM [6,7].

Therefore, the purpose of this study was to compare the efficacy and safety of PGE_2 vaginal insert with those of oxytocin for labor induction. The present study also evaluated whether its use reduces the rate of cesarean delivery in term pregnancies complicated with PROM and low Bishop scores.

Materials and Methods

This study was approved by the ethical committee and institutional review board of Dr Zekai Tahir Burak Women Health and Research Hospital where the study was conducted.

The subjects were recruited from the labor and delivery unit between March 2007 and May 2007. A total of 255 women with term singleton pregnancies, cephalic presentation, PROM ≥ 12 hours, reactive nonstress tests, no previous uterine surgery, and Bishop scores ≤ 6 (unfavorable cervices) were eligible for the study. All subjects gave written informed consent.

Women were excluded from the study if they had more than six previous term pregnancies, vaginal bleeding, hypersensitivity to prostaglandins, asthma, placental pathologies, more than three contractions in 10 minutes, or any other conditions that would contraindicate labor induction.

Four subjects refused to participate in the study for personal reasons; therefore, a total of 240 women were randomly assigned to receive either a vaginal PGE_2 insert or oxytocin infusion. No patients were withdrawn because of maternal side effects such as acute bronchospasm or hypersensitivity reaction.

Although the PGE_2 vaginal inserts are documented to release PGE_2 at a rate of 0.3 mg/hour, the rate differs in the presence of PROM [8]. As recommended by its manufacturer, the PGE_2 insert was left *in situ* for 12 hours, if possible, or removed at the onset of active labor. Active labor was defined as beginning when cervical dilatation was 4 cm.

Oxytocin infusion (5 mU oxytocin in 500 mL of Ringer's lactate solution) was started at a rate of 2 mU/min and increased by 2 mU/min every 20 minutes. If contractions reached a frequency of four per 10 minutes for two consecutive 10-minute periods, the oxytocin dose was not increased further, unless the frequency of contractions diminished. The maximum allowable dose of oxytocin was 36 mU/min.

Uterine contractions were insufficient to sustain active labor in 4.2% (five out of 120) of the subjects treated with PGE_2. Until efficient uterine contractions were achieved, these participants received oxytocin (5 mU oxytocin in 500 mL of Ringer's lactate solution) at a steady infusion rate of 2 mU/min.

Fetal heart rate (FHR) and uterine activity were monitored continuously. The Bishop score was assessed and documented every hour by the same clinician, who also checked whether the vaginal PGE_2 insert was correctly placed and repositioned or replaced the insert when needed. Two researchers together interpreted the traces produced by the external electronic fetal monitors to minimize bias.

Tachysystole was defined as six or more contractions every 10 minutes for two consecutive 10-minute periods, and hypertonus was defined as uterine contraction that lasted ≥ 2 minutes. Oxytocin infusion was decreased and the vaginal PGE_2 insert was removed if tachysystole occurred in the presence of a worrying FHR trace.

Hyperstimulation was described as an exaggerated uterine response with late FHR decelerations or fetal tachycardia (> 160 beats/min) or other worrying FHR changes. In the event of hyperstimulation, the oxytocin infusion was stopped and the vaginal PGE_2 insert was removed, and fetal resuscitation (and tocolysis, if needed) was done.

Despite 12 hours of continuous treatment with the PGE_2 insert, active labor failed to occur in four subjects. To avoid bias and confusion during the interpretation of data, no other method of labor induction methods was used, and for these cases, "failed induction" was reported as the indication for cesarean delivery.

As indicated by the chemoprophylaxis guidelines of the study center, antibiotics were administered to prevent group B streptococcal infections in case PROM lasted for ≥ 18 hours, body temperature was ≥ 38°C, and there was a history of group B streptococcal bacteriuria or previous delivery of a newborn with group B streptococcal sepsis.

Penicillin (5 million U, intravenous (IV), followed by 2.5 million U, IV, every 4 hours until delivery) was the preferred antibiotic. For participants with known hypersensitivity to penicillin, either erythromycin (500 mg, IV, every 6 hours until delivery) or clindamycin (900 mg, IV, every 8 hours until delivery) was preferred. None of the subjects showed any hypersensitivity reactions to the antibiotics for the duration of this study.

All statistical analyses were performed using Statistical Package for Social Sciences version 11.5 software (SPSS Inc., Chicago, IL, USA). Continuous data are expressed as mean ± standard deviation and were

analyzed with two-sample *t* tests. Categorical data were analyzed with χ^2 test. A *p* value of < 0.05 represented statistical significance.

Results

Overall, 120 subjects received a vaginal PGE_2 insert and 120 women received oxytocin infusion. Table 1 shows the preinduction characteristics of the study population. The proportion of nulliparous women were similar in the PGE_2 and oxytocin groups (90/120 [75.0%] *vs*. 80/120 [66.7%]; $p = 0.54$). Table 2 summarizes the clinical outcomes, and Table 3 summarizes the obstetric and neonatal outcomes. There were no cases of intrapartum chorioamnionitis or postpartum endometritis. Table 4 summarizes the selected clinical outcomes for nulliparous women.

Table 1. Preinduction characteristics of the study population*

	PGE_2 ($n = 120$)	Oxytocin ($n = 120$)	*p*
Maternal age (yr)	24.9 ± 5.2	25.0 ± 4.4	0.96
Maternal weight (kg)	70.8 ± 7.7	71.1 ± 9.5	0.92
Maternal BMI (kg/m^2)	27.1 ± 2.8	27.4 ± 3.7	0.57
Gestational age (wk)	38.7 ± 1.4	38.7 ± 1.4	0.75
Parity	0.7 ± 0.9	0.8 ± 1.2	0.21
Preinduction Bishop score	3.77 ± 1.1	3.86 ± 1.5	0.72

**Data are presented as mean ± standard deviation. PGE_2 = prostaglandin E_2; BMI = body mass index.*

Table 2. Clinical outcomes of the study population*

	PGE_2 ($n = 120$)	Oxytocin ($n = 120$)	*p*
Duration of treatment (hr)†	8.5 ± 3.6	8.8 ± 2.5	0.44
Frequency of uterine contractions (/hr)	20.0 ± 10.0	22.0 ± 8.0	0.33
Mean duration of a contraction (s)	58.1 ± 12.2	63.2 ± 13.4	0.38
Bishop score change in 12 hours	5.5 ± 2.4	5.3 ± 2.1	0.88
Induction to active labor onset (hr)	8.5 ± 3.6	4.9 ± 4.1	0.02
Induction to delivery (hr)	9.6 ± 4.7	3.4 ± 1.5	0.02
Uterine hypertonicity	2 (1.7)	0 (0)	0.71
Uterine tachysystole	5 (4.2)	4 (3.3)	0.11
Uterine hyperstimulation	4 (3.3)	2 (1.7)	0.22
Need to cease treatment‡	5 (4.2)	2 (1.7)	0.04
Need for tocolysis	2 (1.7)	0 (0)	0.71

**Data are presented as mean ± standard deviation or n (%); †duration of treatment refers to the duration of time between placement and removal of the vaginal PGE_2 insert or the beginning and termination of oxytocin infusion; ‡the vaginal PGE_2 insert was removed due to a worrying fetal heart rate trace caused by uterine tachysystole and the oxytocin infusion was stopped due to uterine hyperstimulation. PGE_2 = prostaglandin E_2.*

Table 3. Obstetric and neonatal outcomes of the study population*

	PGE_2 ($n = 120$)	Oxytocin ($n = 120$)	*p*
Cesarean delivery	24 (20.0)	22 (18.3)	0.81
Indication for cesarean delivery			
Worrying FHR	15 (12.5)	13 (10.8)	0.88
Cephalopelvic disproportion	5 (4.2)	7 (5.8)	0.81
Failed induction	4 (3.3)	2 (1.7)	0.68
Mean Apgar score at 1 minute	7.0 ± 0.2	6.8 ± 0.6	0.74
Mean Apgar score at 5 minutes	9.0 ± 0.2	8.8 ± 0.6	0.73
Mean birth weight (g)	3,183.9 ± 326.5	3,202.9 ± 402.9	0.79
Admission to NICU	13 (10.8)	20 (16.7)	0.46

**Data are presented as n (%) or means ± standard deviation. PGE_2 = prostaglandin E_2; FHR = fetal heart rate; NICU = neonatal intensive care unit.*

Table 4. Selected outcomes for nulliparous women

	PGE_2 ($n=90$)	Oxytocin ($n=80$)	p
Preinduction Bishop score	3.8±1.4	3.8±1.7	0.88
Bishop score change in 12 hours	5.6±2.7	5.4±2.3	0.80
Induction to active labor onset (hr)	6.9±4.4	3.6±4.4	0.01
Induction to delivery (hr)	9.1±4.6	5.2±3.4	0.03
Cesarean delivery	23 (25.6)	21 (26.3)	0.81
Mean Apgar score at 1 minute	7.3±0.1	6.9±0.5	0.76
Mean Apgar score at 5 minutes	9.1±0.3	8.8±0.4	0.75

**Data are presented as mean±standard deviation or n (%). PGE_2=prostaglandin E_2.*

Discussion

Spontaneous labor is acknowledged to start within 24 hours of the rupture of fetal membranes before the onset of labor in the majority of women [2]. However, early induction of labor can be initiated to reduce the risk of maternal infection and shorten the delivery time in term pregnancies complicated with low Bishop scores and PROM [3].

Although oxytocin is usually preferred to promote labor in term PROM, it was recently proposed that prostaglandins E_1 and E_2 can be administered vaginally to stimulate cervical ripening in term pregnancies complicated with low Bishop scores and PROM [7,9].

PGE_2 is an efficacious agent that shortens the time from induction to delivery, improves success rates and reduces morbidity associated with labor induction. Although PGE_2 may cause abnormal uterine contractions or FHR traces, abnormal psychomotor or physical development has not been reported in children born to mothers given a vaginal PGE_2 insert to stimulate cervical ripening [10].

Local PGE_2 administration can be carried out via vaginal inserts, tablets or gels [11]. It has been reported that vaginal PGE_2 offers a reasonable, effective and reliable option to induce labor in an outpatient setting [12,13]. Yogev et al [13] showed that the induction of labor with a vaginal PGE_2 insert was successful in 169 out of 211 women (80.1%) with post-term pregnancy, without any serious maternal or fetal complications. However, the rate of cesarean section increased significantly in subjects given a vaginal PGE_2 insert. The risk factors related to the patient and labor induction itself were stated as reasons for the excess number of cesarean deliveries in women with prolonged pregnancies [14].

It has been claimed that there was a marginal improvement in patient satisfaction when a slow-release vaginal PGE_2 insert was used instead of vaginal PGE_2 gel [15]. However, Rabl et al [16] showed that vaginal PGE_2 inserts and tablets were similar in terms of efficacy, safety and patient comfort. They also reported that continuous release of PGE_2 could permit controlled induction of labor, and offer easy removal of the drug in the event of uterine hyperstimulation [16].

Some studies have investigated the efficacy and safety of vaginal PGE_2 inserts in term pregnancies complicated with PROM and low Bishop scores. In one double-blind study, 155 nulliparas with PROM and poor cervical score (Bishop score, <6) were treated with either PGE_2 or placebo inserts. PGE_2 inserts significantly shortened the times from induction to active labor onset and from induction to delivery. However, vaginal PGE_2 administration did not significantly affect the cesarean delivery rate or neonatal outcomes [17].

In another clinical trial, a vaginal PGE_2 insert was administered to induce labor in 42 subjects with preterm PROM and 220 women with term PROM who did not enter spontaneous labor after 24 hours of expectant management. As a result, the vaginal PGE_2 insert was effective in the majority of term and preterm pregnancies complicated with PROM and low Bishop scores, without causing any apparent serious maternal or fetal complications. Higher number of PGE_2 tablets used, nulliparity and heavier birth weight were significantly associated with an increased risk of cesarean delivery [18].

In the present study, oxytocin infusion significantly shortened the times from induction to active labor onset and from induction to delivery when compared with those for the vaginal PGE_2 insert. Both parameters were significantly longer in nulliparous women treated with oxytocin in comparison with those given the vaginal PGE_2 insert. The present study also showed that vaginal administration of PGE_2 did not significant affect the rate of cesarean delivery or indications. The rates of cesarean delivery for the PGE_2 and oxytocin groups (20.0% and 18.3%, respectively) were similar to those of the institution calculated for the first 6 months of 2008 (19.2%).

In term pregnancies with PROM, poor cervical scores and no evidence of infection or obstetric complications, the administration of PGE_2 did not significantly affect the establishment of active labor, and reduced the time from admission to delivery, as compared with oxytocin. Concurrent IV administration of low-dose oxytocin with vaginal PGE_2 may improve uterine contractions and cause cervical ripening much more efficiently, such that the cesarean delivery rates and maternal and neonatal adverse effects are reduced [19].

Ramsey et al [20,21] found that the fetal cardiotocographic abnormalities associated with PGE_2 were less frequent and less severe than those associated with PGE_1. However, the present study demonstrated that the changes in FHR were similar in the PGE_2 and oxytocin groups. However, FHR abnormalities were associated with treatment withdrawal in the PGE_2 group rather than in the oxytocin group, indicating potential disadvantages of vaginal inserts.

The randomized prospective design of the present study overcomes limitations of earlier studies by avoiding biased Bishop scores, misinterpretation of FHR traces and neglected minor maternal and fetal complications. Another advantage is the relatively large study population, which included nulliparous and multiparous women. However, the open-label design may limit the power of the present study. The discrepancies among the primary outcomes of the cited publications and the present study might be attributed to differences in the study populations and study designs.

In conclusion, vaginal PGE_2 appears to be a relatively inefficient method of inducing labor compared with oxytocin in term pregnancies with PROM and unfavorable cervices. However, PGE_2 may maintain uterine contractions as effectively as oxytocin once uterine contractions are established. As vaginal PGE_2 are more expensive, it is rational to prefer oxytocin infusion to induce labor in term PROM accompanied with low Bishop scores.

References

1. Wagner MV, Chin VP, Peters CJ, Drexler B, Newman LA. A comparison of early and delayed induction of labor with spontaneous rupture of membranes at term. *Obstet Gynecol* 1989;74:93–7.
2. Mozurkewich EL, Wolf FM. Premature rupture of membranes at term: a meta-analysis of three management strategies. *Obstet Gynecol* 1997;89:1035–43.
3. American College of Obstetricians and Gynecologists. *Practice Bulletin No. 1: Premature Rupture of Membranes*. Washington, DC: ACOG, 1998.
4. Hannah ME, Ohlsson A, Farine D, et al. Induction of labor compared with expectant management for prelabor rupture of the membranes at term. *N Engl J Med* 1996;334:1005–9.
5. Kelly A, Kavanagh J, Thomas J. Vaginal prostaglandin (PGE2 and PGF2a) for induction of labour at term (Cochrane Review). In: *The Cochrane Library, Issue 3*. Oxford: Update Software, 2002.
6. Crane JM, Bennett KA. A meta-analysis of controlled-release prostaglandin for cervical ripening and labour induction. *J SOGC* 2000;22:692–8.
7. Rath W. A clinical evaluation of controlled-release dinoprostone for cervical ripening—a review of current evidence in hospital and outpatient settings. *J Perinat Med* 2005;33:491–9.
8. Lyrenäs S, Clason I, Ulmsten U. In vivo controlled release of PGE2 from a vaginal insert (0.8 mm, 10 mg) during labor induction. *BJOG* 2001;108:169–78.
9. Kozak LJ, Weeks JD. US trends in obstetric procedures, 1999–2000. *Birth* 2002;29:157–61.
10. Mackenzie IZ. Induction of labour at the start of the new millennium. *Reproduction* 2006;131:989–98.
11. National Institute for Clinical Excellence and the Royal College of Obstetricians and Gynecologists. *Induction of Labor: Evidence-based Clinical Guideline*. London: National Institute for Clinical Excellence, 2001.
12. Sennik BK. Outpatient use of a sustained-release PG E2 vaginal insert: a retrospective study. *Today's Ther Trends* 2001;19:77–84.
13. Yogev Y, Ben-Haroush A, Gilboa Y, Chen R, Kaplan B, Hod M. Induction of labor with vaginal prostaglandin E2. *J Matern Fetal Neonatal Med* 2003;14:30–4.
14. Christensen FC, Tehranifar M, Gonzalez JL, Qualls CR, Rappaport VJ, Rayburn WF. Randomized trial of concurrent oxytocin with a sustained-release dinoprostone vaginal insert for labor induction at term. *Am J Obstet Gynecol* 2002;186:61–5.
15. Tomlinson AJ, Archer PA, Hobson S. Induction of labour: a comparison of two methods with particular concern to patient acceptability. *J Obstet Gynecol* 2001;21:239–41.
16. Rabl M, Joura EA, Yucel Y, Egarter C. A randomized trial of vaginal prostaglandin E2 for induction of labor. *J Reprod Med* 2002;47;115–9.
17. Chua S, Arulkumaran S, Yap C, Selamat N, Ratnam SS. Premature rupture of membranes in nulliparas at term with unfavourable cervices. *Obstet Gynecol* 1995;86:550–3.
18. Ben-Haroush A, Yogev Y, Glickman H, Bar J, Kaplan B, Hod M. Mode of delivery in pregnancies with premature rupture of membranes at or before term following induction of labor with vaginal prostaglandin E2. *Am J Perinatol* 2004;21:263–8.
19. Biem SR, Turnell RW, Olatunbosun O, Tauh M, Biem HJ. A randomized controlled trial of outpatient versus inpatient labour induction with vaginal controlled-release prostaglandin E2: effectiveness and satisfaction. *J Obstet Gynaecol Can* 2003;25:23–31.
20. Ramsey PS, Ogburn PL Jr, Harris DY, Heise RH, DiMarco CS, Ramin KD. Effect of vaginal pH on efficacy of the controlled-release dinoprostone vaginal insert for cervical ripening/labor induction. *J Matern Fetal Neonatal Med* 2003;13:250–3.
21. Ramsey PS, Meyer L, Walkes BA, Harris D, Ogburn PL, Heise RH, Ramin KD. Cardiotocographic abnormalities associated with dinoprostone and misoprostol cervical ripening. *Am J Obstet Gynecol* 2005;105:85–90.